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MO Theoretical Studies on Diels-Alder Reactions of α-Allenic Ketones*

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The Diels-Alder cycloaddition reactions between dienes and allenic ketones were studied theoretically using CNDO/2 method. It was found that the reaction is a neutral electron demand type with matrix element control and the reactivity, the regio-and stereo-selectivities can be correctly predicted based on interaction energies calculated with the 4-center FMO formalism.

The Diels-Alder cycloaddition is an important reaction in organic chemistry. The application of perturbation molecular orbital (PMO) theory to this type of reactions based on orbital energies and eigenvector coefficients of reactants has been successful due to the early transition states involved in the concerted cycloadditions.[1,2] Considerable simplification in the PMO calculations has been realized via recourse to using only the frontier orbitals (FMO), without impairing its qualitative predicting ability on the reactivity, the regio-and stereo-selectivities of the Diels-Alder reaction.[3,4] Indeed it has been shown that the principal stabilization of the transition state arises from the HOMO-LUMO interaction which is the closest in energy.[4]

Allenic ketones are known to induce particular orientating effects in their thermal cycloaddition reactions with unsymmetrical dienes and give highly regio-and stereo-selective products, β-alkylidene ketones.[5]

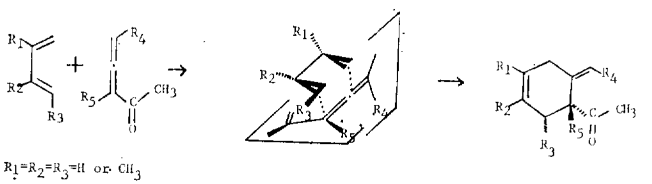
In this work we investigated the reactivity, the regio-and stereoselectivities in the thermal Diels-Alder reactions of allenic ketones, (I)~(III), with some unsymmetrical dienes (Scheme I) using CNDO/2[6] FMO energies and coefficients.

Calculation

The CNDO/2 program[6] has been used throughout in this study. This semi-empirical method of calculation was chosen by the fact that we are primarily concerned with orbital properties, and by the economy of computational expenses. Standard values were adopted for various geometrical parameters.[7] Since the reaction is a concerted $[{}_4\Pi_s+{}_2\Pi_s]$[3a] with neutral electron demand (*vide infra*) type,[8] interaction energies were estimated with 4-center FMO formalism,[9] (1),

$$\Delta E=2\beta^2 \left[\frac{(Ca_{1H}Cb_{1L}+Ca_{2H}Cb_{2L})^2}{|Ea_H-Eb_L|}+\frac{(Ca_{1L}Cb_{1H}+Ca_{2L}Cb_{2H})^2}{|Eb_H-Ea_L|}\right] \tag{1}$$

where a_1, a_2, b_1 and b_2 denote four atoms interacting, and H and L denote HOMO and LUMO. For the cycloaddition of cyclopentadiene to the allenic ketones (I) and (III), secondary orbital interactions,[3a,10] between atoms that do not participate in bond formation have also been considered; a resonance integral (β) of 7 eV for the primary and that of 2.8 eV[11] for the secondary orbital interactions were used in the calculation of interaction energies, ΔE.



$R_1=R_2=R_3=H$ or CH_3
(I) $R_4=R_5=H$
(II) $R_4=H$, $R_5=CH_3$
(III) $R_4=t\text{-Bu}$, $R_5=H$

Scheme I.

Results and Discussion

The FMO properties shown in Table 1 indicate that the substituted dienes used in this work should have no particular orientating effects; the AO coefficients of atoms C_1 and C_4, where the cycloaddition occurs, have similar magnitudes for both FMOs except for those of isoprene ($R_1=CH_3$; $R_2=R_3=H$) HOMO.

On the other hand, significant differences in the HOMO coefficients are noted between the two orthogonal π orbitals, π_y and π_z, of the allenic moiety as shown in Table 2.

The perturbation effects on the two π orbitals caused by the substitution of $COCH_3$ group at C_3 atom are schematically illustrated in Figure 1. The effects of $COCH_3$ group are two

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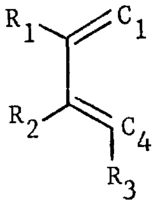
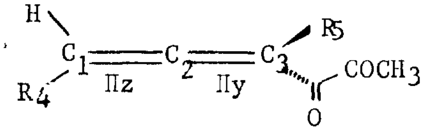
*Part 26 of the series "Determination of Reactivity by MO Theory".

TABLE 1: FMO Energies (a.u.) and AO Coefficients of Substituted 1, 3-Butadienes



R_1	R_2	R_3	HOMO			LUMO		
			C_1	C_4	Energy	C_1	C_4	Energy
CH_3	CH_3	H	0.5551	0.5551	−0.4574	0.5454	0.5454	0.1230
H	H	CH_3	0.5247	−0.5231	−0.4541	0.5299	0.5593	0.1228
CH_3	H	H	0.6186	−0.4931	−0.4698	0.5585	0.5485	0.1243

TABLE 2: FMO Energies (a. u.) and AO Coefficients of α-Allenic Ketones



R_4	R_5	HOMO						LUMO					
		π_z			π_y			π_z			π_y		
		C_1	C_2	Energy	C_2	C_3	Energy	C_1	C_2	Energy	C_2	C_3	Energy
H	H	0.3548	0.1480	−0.4175	0.4770	0.6414	−0.4983	0.6228	−0.6383	0.1847	0.5950	−0.4952	0.1428
H	CH_3	−0.3494	−0.1481	−0.4141	−0.5008	−0.5816	−0.4614	0.6185	−0.6537	0.1996	0.5868	−0.4900	0.1400
t-Bu	H	0.3940	0.2470	−0.3998	−0.4058	−0.5924	−0.4763	−0.6135	0.6161	0.1803	0.6027	−0.4794	0.1538

fold: (1) the carbonyl double bond provides a conjugative chain which causes the decreases in both inter-level spacing and the AO coefficients of the π MOs,[3a] (2) the carbonyl being a strong inductive electron withdrawing group depresses FMO levels[3a] and polarizes the FMOs in such a way that the HOMO (LUMO) lobe size increases (decreases) towards the carbon atom C_3.[3a] The interplay of these two effects is apparent in the FMO levels and lobe sizes of π_y orbital[3a] (Figure 1); as a results of the two effects on FMO levels, the HOMO is slightly raised but the LUMO is lowered significantly.

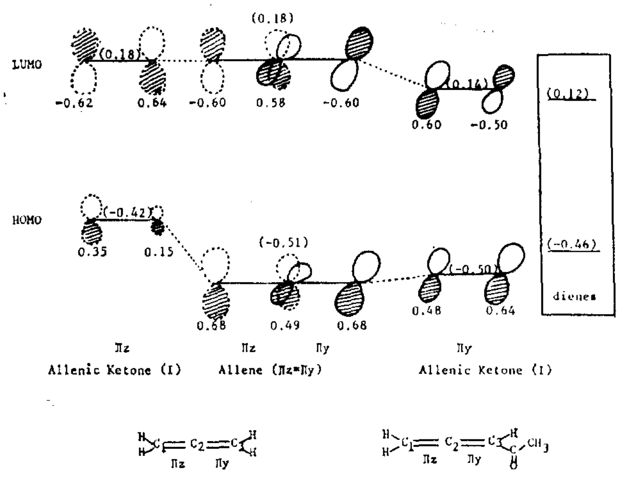


Figure 1. Schematic FMO patterns for the two orthogonal π orbitals, π_z and π_y, of allenic ketone (I) with approximate lobe sizes and levels (in parenthesis, a.u.). FMO levels for dienes are averages of the three substituted butadienes investigated.

The strong inductive effect of the substituent attached to π_y bond is also seen to cause polarization of the π_z FMOs. The HOMO level of π_z is however raised significantly due to the repelling effect of the electron rich π_y orbital, which is orthogonally attached. Since the separation of HOMO (diene) -LUMO (allene) is approximately equal (~0.6 a.u. =16eV) to that HOMO (allene) -LUMO (diene) the cycloaddition will be a neutral electron demand type,[8] for which both interactions between HO (diene) and LU (allene) as well as HO (allene) and LU (diene) are important. Moreover magnitude of HO-LU gaps are relatively large so that the interaction energies, ΔE, are predominantly matrix element (and hence lobe sizes of the FMOs) controlled.[12] It is therefore clear that the cycloaddition of dienes will preferentially occur to the

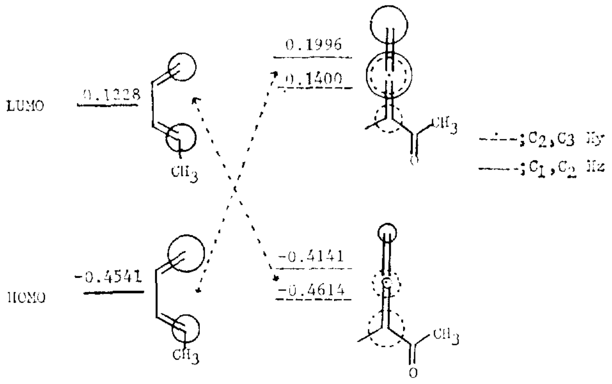
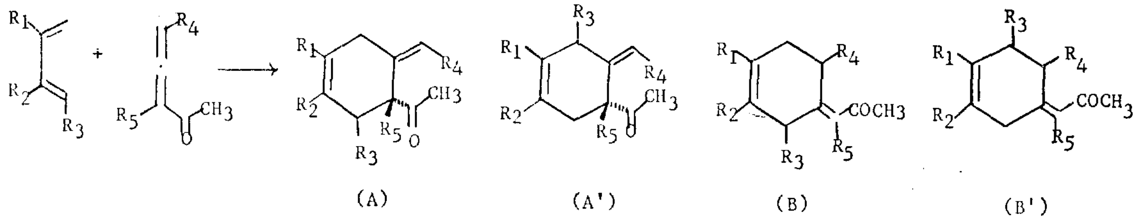


Figure 2. FMO Interaction Schemes Between Piperylene and (II). FMO Levels (a.u.) and Approximate Lobe Sizes are given for π_y (---) and π_z (—).

TABLE 3: Interaction Energies (kcal/mole) Calculated for the Cycloaddition of Dienes to Allenic Dienophiles



R_1	R_2	R_3	R_4	R_5	A	A′	B	B′	Experiment[5]
H	H	CH_3	H	H	95.5	94.7	68.1	68.6	A
H	H	CH_3	H	CH_3	94.2	93.8	67.6	68.1	A
H	H	CH_3	*t*-Bu	H	85.4	84.5	73.5	74.0	A
									A:A′
CH_3	H	H	H	H	101.9	100.1	74.2	74.4	A 95:5
CH_3	H	H	H	CH_3	100.7	98.9	73.5	74.1	A 4:1
CH_3	H	H	*t*-Bu	H	91.6	89.4	79.8	79.6	A 83:17
CH_3	CH_3	H	H	H	100.5		75.0		A
CH_3	CH_3	H	H	CH_3	94.2		67.6		A[a]
CH_3	CH_3	H	*t*-Bu	H	90.2		80.2		A

a: Expected major regioisomer

π_y ($C_2=C_3$) rather than to the π_z ($C_1=C_2$) orbital since the lobe sizes of the π_y are significantly greater than those of the π_z in the HOMO. Furthermore the interaction between the FMOs of the allene π_y and those of diene are more effective than the interaction between those of the allene π_z and diene, since in the former the two interacting FMOs are polarized in the same direction (Figure 2) so that the interacting lobe sizes are the large-large type[3a] while in the latter the interacting lobe sizes are large-small type[3a] which is less effective compared with the large-large interaction.[3a]

The interaction energies calculated for the cycloaddition of substituted dienes to allenic dienophiles are summarized in Table 3. Reference to this table indicates that the adducts formed with $C_2=C_3$ bond, A and A′ are predicted to be favored over the adducts formed with $C_1=C_2$ bond, B and B′. In complete agreement with the experimental results,[5] the adduct A is expected to be the most preferred one in all cases investigated. Stereochemically it has been shown that the diene approaches the reacting π_y bond of the allenic dienophile from the less hindered side leading to a Z substituted form at the exocyclic double bond of the adducts.[5] In the adduct A′ formed with piperylene ($R_1=R_2=H$; $R_3=CH_3$) there is a steric crowding due to the approaching 1-Me group to the out-of-plane allenic H atom of the non-reacting double bond, π_z. It can be seen however that the preference of adduct A relative to A′ in the case of 1-substituted diene is not only controlled by stereochemistry but it is also controlled by the favorable orbital interactions as the ΔE Values in Table 2 indicate. In the cycloaddition of 2,3-dimethylbutadiene to the allenic dienophile (I)~(III), the regioselectivity is determined by the FMOs of dienophile alone, and the major adducts predicted are again in agreement with the experimental results.[5] The results of our calculation in Table 4 reveal the endo-selectivity of allenic ketones in Diels-Alder reaction to cyclic dienes; secondary interaction between the carbonyl carbon and one of the inner carbon atoms, C_3, of cyclopentadiene in the endo orientation (Figure 3) affords extra stabilization energy which is absent or negligible in the exo-form.[3a, 11] Finally the interaction energies in Table 5 show that the reactivities of the allenic ketones should follow the sequence (I)>(II)>(III), according to the substitution of the allenic moiety. This reactivity sequence, which is in full accord with experiment,[5] is also seen to be determined by the general trend of decreasing FMO AO coefficients of atoms C_2 and C_3

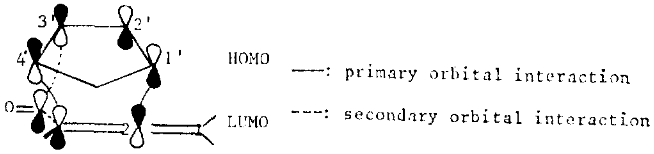
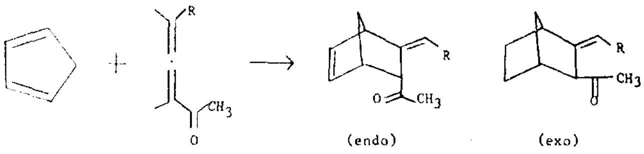


Figure 3. Secondary Orbital Interaction in Diels–Alder Reaction Between Cyclopentadiene and (I).

TABLE 4: Interaction Energies (kcal/mole) Calculated for Endo and Exo Adducts



R	Endo	Exo	Exp Endo: Exo
H	95.2	88.2	71 : 29
t-Bu	84.5	78.3	82 : 18

TABLE 5: Calculated Reactivities (ΔE in kcal/mole) of Allenic Ketones with Unsymmetrical Dienes

dienes	allenic ketones		
	I	II	III
piperylene	95.5	94.2	85.4
isoprene	101.9	100.7	91.6
cyclopentadiene	95.2	—	84.5

(Table 2) in the same direction.

We therefore conclude that the Diels-Alder reaction between diene and allenic ketones is a neutral electron demand type with matrix element control and the reactivity, the regio-and stereo-selectivities can be correctly accounted for using interaction energies calculated with the 4-center FMO formalism.

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Preparation of Allylic and Homoallylic Alcohols Containing Trifluoromethyl Group

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1,1,1-Trifluoro-4-substituted-3-buten-2-ols and 1,1,1-trifluoro-5-phenyl-4-penten-2-ol were prepared by hydromagnesation and palladium catalyzed phenylation in high stereoselectivity.

Introduction

A number of studies have been made on the biologically unique properties of trifluoromethylated organic compounds,[1] and several synthetic methods for these compounds have been developed in recent years. In order to introduce the trifluromethyl group into a carbon skeleton, fluorination of CO_2H by SF_4,[2,3] halogen exchange reactions,[4] and trifluoromethylation[5~7] have been suggested. However, such methods are sometimes accompanied by low reactivity and low selectivity. On the other hand, the use of a proper building block which already has the trifluoromethyl group attached is another promising approach. From this point of view, we have studied the synthesis of trifluoromethylated difunctional compounds.

Recently, we have reported the synthesis of 3-hydroxypropionic esters, allylic alcohols and homoallylic alcohols containing trifluoromethyl group, produced by the reaction of α,α,α-trifluoroacetaldehyde with organometals under ultrasonic irradiation.[8] In our continuing studies on the synthesis of building blocks containing the trifluoromethyl group, we here report the synthesis of substituted allylic and homoallylic alcohols containing trifluoromethyl group, which are interesting intermediates for heterocycles expected to be bioactive pharmaceuticals and agrochemicals.

Results and Discussion

Hydromagnesation of 1,1,1-Trifluoro-4-substituted-3-butyn-2-ol. We have attempted to design a synthetic route for α-trifluoromethyl allylic alcohols as shown in Scheme 1. The first step in Scheme 1 is to react lithium acetylides with α, α, α-trifluoroacetaldehyde at -78 °C to yield the corresponding 1,1,1-trifluoro-4-substituted-3-butyn-2-ol in good yield. Various spectral data that support the above structures are given in Table 1.